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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,099	03/19/2004	Chunhui Xu	099/004P	7715

22869 7590 07/13/2006

GERON CORPORATION
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,099	XU ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *1, 9, 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-16 are under consideration.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant claims priority to Non-Provisional Application No 10/193,884 (f.d.-7/12/2002) and Provisional application numbers 60/322,695 (f.d.-9/10/2001) and 60/305,087 (f.d.-7/12/2001).

The instant invention is drawn to a method of generating cardiomyocytes of cardiomyocytes precursors from primate pluripotent stem (pPS) cell comprising culturing pPS cell in embryoid bodies to induce differentiation and isolate cells that have a cardiomyocytes phenotype. This aspect of the invention is encompassed by claims 1-10. These claims are also disclosed in all of the priority documents. Therefore, for claims 1-10, Applicant has complied with conditions for receiving the benefit of an earlier filing date of 7/12/2001.

Claims 11-16 are drawn to a method of enriching cardiomyocytes obtained from the methods describe in claims 1-10. The method of these claims is only adequately disclosed in the instant application. Therefore, Applicant has not complied with conditions for receiving benefit of an earlier filing date for claims 11-16 and therefore the filing date (3/19/2004) is the effective filing date for these claims.

Information Disclosure Statement

3. The information disclosure statement filed 1/17/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner was able to retrieve and consider the U.S. patents and WO documents listed, but copies of the non-patent literature documents could not be located.

Reference AR and BA were not considered and crossed out because AR was not provided and BA was illegible. If Applicant would like these references to be considered, they should be submitted in a new IDS.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Page 17, line 39 contains a hyperlink which should be removed.

5. The use of the trademarks has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

6. Claim 1 is objected to for reciting in b) ""differentiate into areas". Cells do not differentiate into "areas". They differentiate into cell with a differentiated phenotype. In the instant case, the cells differentiated into cells that undergo spontaneous contraction.

Claims 9 and 10 for reciting "a medium containing" whereas this should recite "a medium comprising". The term "containing" is closed claim language inferring that the medium only has the factors claimed. The specification suggests this is not the intent of Applicant and furthermore the cell would not survive in such medias. Therefore, open claim language "comprising" would be more appropriate in the instant claims.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating cardiomyocytes or cardiomyocytes precursor cells from human embryonic stem (hES) cells obtained from a human blastocyst comprising initiating differentiation of the hES by forming embryoid bodies (EB) in suspension culture, wherein differentiated cells of the EB undergo spontaneous contraction, harvesting the differentiated cells that demonstrate spontaneous contraction, further separating the harvested cells into factions by density centrifugation, and isolating the cells that express cardiac tronin I (cTnI), cardiac troponin T (cTnT), atrial natriuretic factor (ANF) or α-cardiac myosin heavy chain (MHC), thereby generating a cell composition comprising cardiomyocytes or cardiomyocytes precursors, does not reasonably provide enablement for a method

comprising initiating differentiation of any pPS cell, collecting any differentiated cells and generating a cell composition containing cardiomyocytes or cardiomyocytes precursor cells only. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The instant invention claims initiating differentiation of pPS cells via the formation of EB. The instant specification provides guidance disclosing methods to culture hES

cells to form EB (par [197] to [202] of the published application). However, the specification does not provide guidance on how to produce EB with any other pPS. The art does not disclose method of generating EB with any other cell type other than embryonic stem (ES) cells. Given that the specification and the art does not provide guidance disclosing methods of generating EB from any other cells type other than ES cells, the instant specification only supports ES cell and not pPS cells.

The instant invention claims a method comprising generating a cell composition containing cardiomyocytes or cardiomyocytes precursor cells only. However the art suggest that obtaining a homogenous cell population following the differentiation of stem cells in not possible and would be highly unpredicatable.

Verfaillie *et al.* [**Hematology** (Am Soc Hematol Educ Program). 2002;:369-91] who review the state of the art of stem cells at the time of filing, teach, that, with regard to the directed differentiation of ES cells, "Many proposed applications of human ES cells are predicated on the assumption that it will be possible to obtain pure populations of differentiated cells from the ES cultures. It might be envisioned that in order to achieve this one would treat ES cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice, that has not proven possible with the mouse system." See p. 278, 2nd column, Differentiation in vitro. They further teach that a range of approaches have been attempted to produce a highly homogenous population of differentiated cells from ES cells, for example, relying upon the spontaneous differentiation of the ES cells to embryoid bodies. However, embryoid bodies contain a range of differentiated cells, which is a recognized limitation of directed

differentiation of ES cells. Verfaillie teach that the ES cells can be treated with particular agents/factors that can drive differentiation along a specific lineage (see p. 379, 1st column, 1st full ¶. However, it is clear that directed differentiation of ES cells to generate a particular cell type of interest is unpredictable. Thus, specific guidance must be provided to enable the claimed invention. Therefore, any cell composition produced by driven differentiate as claimed will also comprise a percentage of other cells types. Since the art suggest that a homogenous cell composition is not possible and the art does not provide guidance to overcome these obstacles presented in the art, the instant specification does not enable a method of generating a cell composition containing cardiomyocytes or cardiomyocytes precursor cells only.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat.

App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 1 and 16 recite the broad recitation "primate pluripotent stem (pPS) cells", and the claim also recites "obtained from a human blastocyte", which is the narrower statement of the range/limitation. Human embryonic stem cells can be the only type of pPS cell that can be isolated from human blastocysts. However, the breadth of pPS cell includes many other non-human and human stem cells. Therefore, it is unclear which breadth Applicant is claiming.

Regarding claims 3 and 4, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The term "about" in claims 6 and 13 is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims more specifically recites "containing" or "contains about 20% serum". The metes and bounds of "about 20% serum" is relative and therefore the metes and bounds are unclear.

Furthermore, this recitation is in conjunction with the term "contains" which is closed claim language inferring a specific limitation further rendering unclear intentions of the claims.

Claim 1 and 8 recite "according to". "According" to accord is defined as the following:

1. To cause to conform or agree; bring into harmony.
2. To grant, especially as being due or appropriate: *accorded the President the proper deference.*
3. To bestow upon: *I accord you my blessing.*

http://dictionary.reference.com/search?q=according

Because "according" only implies a level of agreement with something, in the instant case other claims, the metes and bound of "according" are unclear and do not further limit the instant claims.

Claims 9 and 10 recite the limitation "the collected cells". There is insufficient antecedent basis for this limitation in the claim. The cells are collected in several steps of the method. Therefore, it is unclear which set of collected cells should be cultured in the claimed medium.

Claims 2 recites a trademark Matrigel™. Trademarks can not be claimed.

Claims 2-16 are directly or indirectly dependent upon claims that were deems indefinite, therefore the dependent claims are rendered indefinite and rejected under 112 2nd paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al. (Circ Res 91:501-508, 2002; of record).

The instant invention is drawn to a method comprising initiating differentiation of pPS cells by forming EB in suspension culture wherein the differentiated cells undergo spontaneous contraction, harvesting the differentiated cells, enriching the cardiomyocytes by density centrifugation, and isolating the cells that express cardiac specific markers, cTnI, cTnT, ANF, or MHC.

Xu et al. discloses a method of inducing hES cells to differentiate into by culturing clumps of hES cells in suspension culture to induce EB formation in 20% serum. After 4 days, EB were transferred to gelatin coated plates and further cultured in a nutrient media containing 20% fetal bovine serum and then examined for the presence of beating cells (par bridging p. 501 and p. 502). Xu et al disclose that spontaneously contracting cells were present in clusters in ~25%of EB at day 8 to 70% of the EB at day 16, therefore at the start of the any further enrichment by percol gradient at least 20% of the cells were identified as cardiomyocytes. Differentiated hES cells containing beating cells were dissociated, resuspended in differentiation media, loaded onto a Percoll gradient, and subjected to centrifugation (p. 502, par 2).

The specification describes the enrichment procedure as such:

After settling for 5 min, the cell suspension was loaded onto a layer of 40.5% Percoll.TM. (Pharmacia) (.about.1.05 g/mL) overtop of a layer of 58.5% Percoll.TM. (.about.1.075 g/mL). The cells were then centrifuged at 1500 g for 30 min. After centrifugation, cells on top of the Percoll.TM. (fraction I) and a layer of cells in the interface of two layers of Percoll.TM. (fraction II) were collected. The collected cells were washed, resuspended in the differentiation medium, and seeded at 10.sup.4 per well into chamber slides. [207]

and the instant claims are drawn to separating the harvested cells by "distributing cell in the population according to their density and collecting the cells between ~1.05 and ~1.075 g/mL.

Xu et al. discloses the same gradient and centrifugation and collecting the same cell form the 6 fractions between these gradients. Xu et al also discloses the use of MHC to isolate myocardiocytes that are concentrated in fractions 3 and 6 (see Figure 4). They also disclose identifying and isolating cardiomyocytes using cTnI with 20 to 40% enrichment fraction 3 and 50 to 70 % enrichment in fraction 6. They further demonstrate that these cells express cTnT by immunocytochemistry and ANF by RT-PCR (figure 2 p. 503). Therefore an artisan would know that they could use these markers to isolate and enrich the populations as well. Furthermore, all of these data are discloses in the specification of the instant application, therefore, coinciding with the intent of the instant application.

The instant invention claims further rounds of enrichment by collecting cells that are present in clusters and reculturing them and subjecting them to further rounds of

selection by spontaneous contraction and the same cardiac specific markers. The instant claims specify at least 60 % of the clusters undergo spontaneous contraction after reculturing. Again, Xu et al demonstrated this can be obtained by culturing for a longer duration. The instant invention claims further rounds of reculturing following marker identification present in 20 percent of the cells to final production of 80% of the cells. Examples 10 and 11 in the specification describe these procedures for enrichment of myocardiocytes, however, they do not provide any new or different step than were originally presented in Xu et al and describe successive rounds of culture and selection. Therefore it would be inherent to the method disclosed in Xu et al, that further rounds of culture and selection would result in an enrichment of the cells population to upward of 80+%. Such yields are also disclosed by Xu et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doevendans et al (J Mol Cell Cardiol 32:839-851, 2000, of record), Sugi and Lough (Dev Biol 168:567-574, 1995; of record), Murrell et al. (Mech Aging Dev 77(2):abstract, 1994) Takahashi et al (J Cardio Pharm 41(5): 726-733), Nair and Nair (Indian J Exp Biology 35(5):abstract) and (Makino et al. J clin Invest 103(5):697-705), in view of Kehat et al (J Clin Invest 108(3):407-414, 2001, of record).

The instant invention is drawn to a method comprising initiating differentiation of pPS cells by forming EB in suspension culture wherein the differentiated cells undergo spontaneous contraction, harvesting the differentiated cells, enriching the cardiomyocytes by density centrifugation, and isolating the cells that express cardiac specific markers, cTnI, cTnT, ANF, or MHC. Narrowing claims specify that the EB be plated on a surface coated with gelatin or Martigel, differentiated in the presence of a nucleotide analog that affects DNA methylation such as 5-aza-deoxy-cytidine, be differentiated in a growth environment comprising morphogen, such as activin and other growth factors. Narrowing embodiments also specify that the cells be further subjected to density centrifugation, that the collected cells be cultured in medium containing a compound capable of forming a high energy bond, an acyl group carrier molecule, and

a cardiomyocytes calcium channel modulator and/or containing creatine, carnine, or taurine.

Doevendans et al teach a method of initiating differentiation of mouse ES cells by forming EB in suspension culture wherein the differentiated cells undergo spontaneous contraction, harvesting the differentiated cells, enriching the cardiomyocytes by density centrifugation, and isolating the cells that express cardiac specific markers using immunochemistry (p. 840, par bridging col 1 and 2). They specifically use a Percoll density gradient wherein cell are collected from between layers that were 1.09 g/ml to 1.07 g/ml (col 2, lines 18-24). Cell were cultured on gelatin in the presence of 20% fetal calf serum (col 2, lines 25-30). Immunocytochemistry with atrial and ventricular myosins was also used to verify the cardiomyocytes lineage of the cells (p. 841, col 2, par 3). They do not teach culturing in activin and other growths, differentiated in the presence of a nucleotide analog that affects DNA methylation such as 5-aza-deoxy-cytidine, cardiac specific markers, cTnI, cTnT, ANF, or MHC, or culturing in medium containing a compound capable of forming a high energy bond, an acyl group carrier molecule, and a cardiomyocytes calcium channel modulator. They do not teach the use of pPS cells.

Makino et al teaches a method of driving stem cell from bone marrow to obtain a myocardiocyte linage by culturing with 5-azacltidine (p. 698, col 1, par 1, lines 15-24). Makino et al teaches that 5-azacytidine is a cytosine analog capable of altering the expression of gene that regulate differentiation (p. 697, col 2, lines 19-21). They teach more specifically, treatment altered cardiomyocytes associated gene MEF2A and MEF2D and drives cells with a fibroblast-like phenotype to obtain cardiomyocytes-like

phenotype with spontaneous contractions and myotube-like structures in 30% of the cells (see abstract). Given that they demonstrated ability to drive stem cells to a cardiomyocytes linage, they also provide motivation to use 5-azacytidine to induce differentiation. Makino et al do not teach culturing in activin and other growths, cardiac specific markers, cTnI, cTnT, ANF, or MHC, or culturing in medium containing a compound capable of forming a high energy bond, an acyl group carrier molecule, and a cardiomyocytes calcium channel modulator. They do not teach the use of pPS cells.

Sugi and Lough teach a method of culturing embryonic precardiac myocytes explants in the presence of activin-A, FGF-2, and insulin (p. 568, Germ Layer Explantation section). They teach that culturing with these factors resulted in explants that exhibited synchronous contractions and expressed cardiac RNA (see abstract). These data demonstrate that culturing with activin-A, FGF2 and insulin drives differentiation in an embryonic cardiomyocytes precursor cell and therefore provides motivation to include in cultured to generate cardiomyocytes from embryonic cells. They do not teach differentiating in the presence of a nucleotide analog that affects DNA methylation such as 5-aza-deoxy-cytidine, cardiac specific markers, cTnI, cTnT, ANF, or MHC, or culturing in medium containing a compound capable of forming a high energy bond, an acyl group carrier molecule, and a cardiomyocytes calcium channel modulator. They do not teach the use of pPS cells.

Murell et al teaches cDNA cTnI, cTnT, ANF, or MHC. They teach a cDNA can be used as identifying cardiac differentiation markers. The also state that these markers, when used as a group provide a more definitive indication of authentic cardiac cellular

differentiation (see abstract), which provides a motivation for their use in methods of generating cardiomyocytes. They do not teach culturing in activin and other growths, differentiated in the presence of a nucleotide analog that affects DNA methylation such as 5-aza-deoxy-cytidine, or culturing in medium containing a compound capable of forming a high energy bond, an acyl group carrier molecule, and a cardiomyocytes calcium channel modulator. They do not teach the use of pPS cells.

Takahashi et al teaches a method of culturing rat neonatal cardiomyocytes in media containing taurine. They reported that culturing rat neonatal cardiomyocytes in the presence of taurine under ischemic conditions was protective against necrosis and apoptosis. These data suggest that adding taurine to a culture that generates cardiomyocytes is protective against cell death and therefore promote the presence of more viable cardiomyocytes.

Nair and Nair teach teach a method of culturing cardiomyocytes in the presence of calcium ion chelators that improves the yield of ventricular myocardial cells (see abstract). Nair and Nair do not teach a method of generating myocardiocytes from pPS cells.

None of these methods specifically identify a medium containing a compound capable of forming a high energy bond and an acyl group carrier molecule, however, these factors would be inherent to Doevendans et al, Makino et al, and Sugi and Lough because if these factors were not present in the media, the cardiomyocytes would not have the nutrient materials necessary to undergo spontaneous contraction and given that this occurs in all of these references, it is inherent that a compound capable of

forming a high energy bond and an acyl group carrier molecule was present in the method.

The instant methods disclosed above to not specifically teach the culture of pPS cells to generate cardiomyocytes. However, Kehat et al. teaches a method of generating cardiomyocytes from hES cells that utilize the same steps and same marker as disclosed in Doevendans et al and Murell et al and sucessfully produce human cardiomyocytes using that same methodology. Given that the same methodology was used to generate human cardiomyocytes as Doevendans et al and the claimed method, it would be inherent that the method described by Doevendans et al would have produced human cardiomyocytes from pPS cells at the time of filing.

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the methods of generating cardiomyocytes from ES cells by Doevendans et al. to include the differentiating factors of 5-aza-deoxy-cytidine, Activin, and FGF2 and use cardiac specific markers, cTnI, cTnT, ANF, or MHC, to isolate the cells. Sugi and Lough and Makino et al provide the motivations for the use of 5-aza-deoxy-cytidine, Activin, and FGF2 as differentiation factors because they have been demonstrated to drive stem cells to differentiate into a cardiomyocytes lineage. Murell et al provide motivation for the use of cTnI, cTnT, ANF, or MHC to isolate myocytes because they are indicative of authentic cardiac cellular differentiation. Furthermore, it also would have been obvious to an artisan of ordinary skill to combined these with a reasonable expectation of success because all of these methods have been well established in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 2, 4, 7, 8, are11-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-12 of copending Application No. 11/086,709. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions have overlapping scope.

Both inventions are drawn to a method of differentiating pPS, derived from human blastocysts, in to cell of a cardiomyocytes lineage. The instant application specifies generating cardiomyocytes or cardiomyocytes precursor cells, whereas the copending application more broadly claims cells of cardiomyocytes lineage. The instant

method specifically claims that the pPS cell be differentiated by forming EB in suspension culture and culturing the differentiated cells into areas that undergo spontaneous contraction. The copending application specifies plating the pPS cells without the formation of EB directly onto a solid surface comprising a substrate to which cardiomyocytes lineage cells adhere and permitting the cell to establish onto the substrate. Although not directly stated, these limitations of the copending application can encompass an EB suspension culture where only the cardiomyocytes linage cells adhere to the solid surface, which can also be encompassed by the limitations described in the instant application. Both inventions specify a gelatin substrate, but the instant application also encompasses Matrigel whereas the copending application also encompasses fibronectin. Both applications specify culturing with activin, but the instant application broadly claims the inclusions of other growth factors, whereas the copending application more specifically claims culture with Activin A and BMP-4. Both applications claim an enrichment step that involves separating harvested differentiated further according to their density and isolating cardiomyocytes with the use of cardiac specific markers MHC (claim 16 of the instant invention, claim 1 of the copending). The instant application more narrowly specifies that this step be done by gradient centrifugation wherein the cells are present in the fractions between 1.05 and 1.075 g/mL. Both inventions also enrich cells and produce more cells by a series of reculturing the cell clusters. Claim 9 of the copending application is identical in scope to claims 11 anf 15 of the instant application. Claims 10 and 11 of the copending application are identical to

claims 12 and 13, respectively, of the instant application, and claim 12 of the copending application is identical in scope to claim 14 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1-5, 7, 8, 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12-18, and 20 of copending Application No. 11/040691. Although the conflicting claims are not identical, they are not patentably distinct from each other because they have overlapping scope.

Both inventions are drawn to a method of differentiating pPS, derived from human blastocysts, in to cell of a cardiomyocytes lineage. The instant application specifies generating cardiomyocytes or cardiomyocytes precursor cells, whereas the copending application more broadly claims cells of cardiomyocytes lineage. Both cases specify initiating pPS cell differentiation by the formation of EB. The instant claims specify that the EB culture be a suspension culture. The instant application bradly claims culturing in a growth environment compring activin and two or more growth factors, more specifically a member of the TGFbeta family and IGF (claims 4 and 5), whereas as the copending claims more narrowly specifiy Activin A with BMP-4 or other members of the TGFbeta family (claims 2-9). Both inventions specify a gelatin substrate, but the instant application also encompasses Matrigel (claims 2) whereas the copending application also encompasses laminin (claim 13). Claim 3, 7, and 8 of the instant invention is identical to 13, 14, and 15, respectively. Claim 10 of the instant

invention and claim 17 of the copending application both claim supplementing the culture media with creatine, carnitine, or taurine. Both applications specify collecting the spontaneously contracting cells and isolating cells that express cTn1, cTnT, ANF, and/or MHC. However, the copending application more narrowly specifies that the instant 5% of the cells should have spontaneous contractile activity (claim 20).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1, 2, 6-8, and 11-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 and 16 of copending Application No. 11/085,899. Although the conflicting claims are not identical, they are not patentably distinct from each other because they have overlapping scope.

Claim 10 of the copending application is almost identical to claim 1 is its recitation of the method steps except it includes MHC as an additional endogenous gene claims. The scope of claim 10 of the copending application is identical to that of claim 11, where the cardiomyocytes are further subjected to a series of resulting of the cells clusters to obtain more cardiomyocytes. Claim 6-9 of the copending application is identical in scope to claim 11-16 of the instant claims, except it does not specify the steps by which the cell population expressing the claimed endogenous genes are obtained. Claim 16 of the instant application is identical to claim 6 in scope except that claim 16 more narrowly requires 80% of the clusters undergo spontaneous contraction whereas claim 6 more broadly requires 50%. The claims that specify the substrate and the conditions of separating by density are identical in these applications. Claims 1-5 of

the copending application are product by process claims that specify that method of claims 6-9 are already discussed above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Marcia S. Noble